PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K	A2	(11) International Publication Number: **WO 97/46208** (43) International Publication Date: 11 December 1997 (11.12.97)

(21) International Application Number: PCT/US97/11963

(22) International Filing Date: 9 June 1997 (09.06.97)

(30) Priority Data:
08/657,915 7 June 1996 (07.06.96) US

(71) Applicant: MT. SINAI SCHOOL OF MEDICINE OF THE CITY OF NEW YORK [US/US]; One Gustave L. Levy Place, New York, NY 10028-6574 (US).

(72) Inventor: WEI, Huachen; 114-15 Union Turnpike, Forest Hills, NY 11375 (US).

(74) Agent: CLARK, Richard, S.; Brumbaugh, Graves, Donohue & Raymond, 44th floor, 30 Rockefeller Plaza, New York, NY 10112 (US).

(81) Designated States: AU, CA, GB, IL, JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: GENISTEIN AS A PREVENTIVE AGAINST ULTRAVIOLET INDUCED SKIN PHOTODAMAGE AND CANCER

(57) Abstract

A method of inhibiting the harmful effect of UVR exposure to the human skin comprising topically applying a therapeutically effective amount of genistein to the skin at a time sufficiently close to the time of UVR exposure to inhibit UVR-induced damage to the skin. The genistein appears to act as a chemo preventative agent since it has no appreciable sun blocking effect. The genistein may be mixed with a variety of carriers and skin treatment compositions.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

Description

Genistein as a Preventive Against Ultraviolet Induced Skin Photodamage and Cancer

Background of the Invention

The present invention relates to the prevention or treatment of skin damage and skin cancer, and in particular to ultraviolet radiation (UVR)-induced skin photodamage and cancer.

It is well documented that long term exposure to ultra-violet light, e.g., sunlight, will damage the skin. Such UVR-induced skin damage includes premature aging, as well as various skin cancers, for example, basal cell carcinoma, squamous carcinoma and malignant melanoma.

While the damaging effects of UVR are known, the recreational and occupational exposure to UVR is a day-today fact of life. While some people successfully minimize their exposure, others are either unwilling or unable to do so. For these people, exposure was either accepted as a risk, however unreasonable, or at best was prevented with various heretofore known sun blockers.

Sunscreens or sun blockers physically block the UV rays and thereby lessen the amount of UV light that would otherwise reach the skin. Known products include para aminobenzoic acid (PABA) as well as certain metal oxides. The evaluation of such products is discussed in Harry's Cosmeticology, Seventh Ed., pp. 222-263.

The above use of UVR blocking agents is to be distinguished from the use of chemopreventative agents against cancer or skin degenerative processes. Chemopreventative agents function to prevent or alter the various cellular or molecular carcinogenic processes that ultimately lead to tumor growth and the like.

The typical chemopreventative agents, on the other hand, must be administered into the body, such as by oral ingestion, or by injection.

With respect to orally ingested anti-cancer agents, epidemiological studies have shown that consumption of soybean-containing diets have been associated with lower incidence of certain types of human cancers. In particular, the soybean isoflavone "genistein" has been associated with the chemoprevention of cancer. See Wei et al., Inhibition of tumor promoter-induced hydrogen peroxide production in vitro and in vivo by genestein, Nutrition and Cancer 20:112, 1993; Antioxidant and Antipromotional Effects of the Soybean Isoflavone Genistein, Wei et al., Proceedings of society for Experimental Biology and Medicine, 208: 124-130, 1995.

The purification of genistein from soy products, e.g., soy molasses, is known. See Peterson et al., Genistein inhibition of the growth of human breast cancer cells: independence from estrogen receptors and the multidrug resistance gene, Biochem Biophys Res Commun 179: 6616671 1991, incorporated herein by reference.

Summary of the Invention

In accordance with the present invention, it has been discovered that genistein may be used as a topical chemopreventative agent against the adverse effects of UVR on the skin. Genistein may be topically applied, alone or co-administered with other medications, to lessen or prevent UVR-induced skin sunburns, premature aging, and skin cancer.

Genistein is uniquely suitable as a topically applied chemopreventative agent in that it is a natural product having no observed adverse effects or toxicities in humans. The physical and chemical properties of genistein are appropriate for a topical skin agent, i.e., it has high lipid solubility and easily penetrates the skin.

Data suggests that genistein exhibits potent and stable antioxidant activities. It scavenges reactive oxygen species and increases antioxidant enzymes in mouse skin tissue. Thus it may serve to delay skin aging and inhibit skin tumorigenesis.

Since genistein also relieves chemical carcinogen-induced skin inflammation, it may serve as an antiinflammatory agent on chemical skin irritations.

Genistein's ability to inhibit chemical carcinogen-induced protooncogene expression and tumorigenesis permits its use as a chemopreventive agent against chemical-induced carcinogenesis of skin. Genestein's ability to quench UVR-induced oxidative DNA damage in vitro and in cell culture makes it a useful topical agent for inhibiting the initiation of skin photocarcinogenesis. Moreover, genistein has been shown to suppress UVR-induced protooncogene expression (i.e., in mouse skin) and phosphorylation of the epidermal growth factor receptor in human keratinocytes, thus indicating genistein's ability to inhibit the promotion of skin photocarcinogenesis.

While the possible UVR blocking effect of genistein cannot be entirely discounted, it is genistein's chemopreventive properties that are of particular interest. Thus while the use of a conventional sun-blocking product connotes exactly what the name implies i.e., that the sun actually be blocked from reaching the skin -- a chemopreventative product need only be typically applied in such a manner that the chemopreventative mechanism function in a therapeutically effective manner.

It is therefore contemplated that such compositions be applied even on the assumption that otherwise harmful UVR or chemical agents will have reached the skin. Included would be the topical application before, during or even after exposure to UVR or other harmful agents, so long as the desired chemopreventive effect can take place to a therapeutically effective extent.

Compositions according to the invention can also be combined with compositions that have other UVR-blocking or antiaging properties. They can also be combined with carriers that will facilitate penetration into the skin, such as DMSO, ethanol, propylene glycol, etc. Finally, the compositions can be combined with compositions that have other cosmetic or medicinal properties, such as skin creams, make-up preparations, tanning lotions or the like.

As noted above, various properties, effects and mechanisms of genistein have been disclosed by the present inventor, although not necessarily as part of the prior art. The above-referenced publications, as well as the prior art and non-prior art publications cited therein, are incorporated herein by reference for purposes of providing background. While some of the properties or mechanisms discussed therein may provide some explanation of the beneficial effects obtained according to the presently disclosed topical uses of genistein, other mechanisms or combinations of mechanisms may be involved.

Brief Description of the Drawings

The description of the preferred embodiments is further explained below with reference to the figures, wherein:

Figure 1 is a photograph of a patient's back after UVB exposure as described in Example 1.

Figure 2 is a photograph of the gel electrophoresis as described in Example 3.

Figure 3 is a photograph of the gel electrophoresis as described in Example 4.

Figures 4 and 6 are photographs of the gel electrophoreses as described in Example 5.

Figure 5 is a graph showing the quantitation of transcript levels, also as described in Example 5.

Detailed Description of the Preferred Embodiment

Various topical uses of genistein are contemplated by the present invention. These include the prevention or treatment of the affects of UVR on the skin, e.g. premature aging and cancer. Also contemplated is the topical application of genistein as an antiinflammatory agent for chemical skin irritation. These uses are discussed in conjunction with the following examples.

Example 1

An experiment was performed to measure the effect of genistein on UV-induced skin erythema.

A human subject was subjected to UVB doses ranging from 0 to 90 mJ/cm^2 in three separate "lanes." These Lanes are depicted in Figure 1.

In Lane 1, the patent was first topically treated with a 5 μmol solution of genistein per cm^2 of skin. The genistein was applied in a 5:95 DMSO:acetone carrier.

In Lane 2, no pre-treatment was given.

In Lane 3, the patient was topically treated with only the DMSO:acetone carrier.

As can be seen from Figure 1, Lane 1 shows virtually complete protection against skin erythema with the genistein. Both of Lanes 2 and 3 (i.e., no treatment; carrier only) showed UVB dose-dependent induction of skin erythema.

While the mechanism by which genistein inhibited erythema is unknown, the mechanism appears to be independent of the "sunscreen" effect. This was confirmed by dissolving up to 100 MM genistein in water. No blocking effect of UVB was observed in the genistein solution as compared to the water alone. Methods for testing the sunscreen effect of various compositions are discussed in Harry's Cosmeticology, Id.

Example 2

An experiment was conducted to determine the effect of genistein dosage on skin erythema inhibition.

The subject was uniformly exposed to a UVB dose of 45 mJ/cm^2. The genistein dosage was varied from a high of 5 μmol to a low of 0.0 μmol per cm^2 of human skin (i.e. , 0.0 μmol; 0.05 μmol; 0.1 μmol; 0.5 μmol; 1.0 μmol; 5.0 μmol). A striking inhibition of erythema was observed at the 0.1 μmol level and above. As with Example 1, this inhibiting effect appears to be independent of the sunscreen effect as confirmed by the apparent lack of UV blocking even at a 100 μmol genistein in water.

Example 3

Ultraviolet B (UVB)-induced MRNA, expression of protooncogenes c-*fos* and c-*jun* mRNA in the shaven skin of Sencar mice was characterized using the Northern hybridization. When mice were irradiated with the defined doses of UVB (5 and 15 kJ/m^3), both c-*fos* and c-*jun* expression were induced in a time-dependent fashion. The level of c-*fos* and c-*jun* mRNA increased immediately and reached a maximum 1 h after UV irradiation. Expression of *c-fos* and c-*jun* appeared to be independent of UV dose.

Topical application of genistein (20 μmol) 1 h prior to UV radiation substantially inhibited UVB-induced c-*fos* and c-*jun* expression induced by a low dose of UVB (5 kJ/m^2). At a higher dose of UVB radiation (15 kJ/m^2), genistein still substantially blocked UVB-induced c-*fos* expression, but had little effect on c-*jun* expression. The inhibition of UVB-induced protooncogene expression *in vivo* by genistein may be related to the signal transduction pathways because genistein was shown to downregulate UVB-induced tyrosine phosphorylation of epidermal growth factor receptor in cell culture, and mitogen protein kineses in mouse skin. The inhibitory effect of genistein on UV-induced protooncogene expression suggests its potential antipromotional role in photocarcinogenesis. The results of this experiment are shown in Figure 2. Lane 1 depicts no UV; Lane 2 depicts UV at a dosage level of 5 kJ/m^2 (no treatment); Lane 3 depicts 20 μmol genistein applied one hour prior to 5 kJ/m^2 UV exposure; Lane 4 no UV; Lane 5 depicts 15 kJ/m^2 (no treatment); Lane 6 depicts 20 μmol genistein applied one hour prior to exposure at a UV dosage 2 of 15 kJ/m^2.

The results of this study were presented at the '96 Society of Investigative Dermatology in Washington, D.C., May 1-5, 1996. An abstract was published in Journal of Investigative Dermatology, 106(4): 856, 1996.

Example 4

A procedure similar to that of Example 3 was followed except that the genistein (20 μmol) was applied immediately after exposure to UVR (15 kJ/m^2).

As shown in Figure 3, Lane 1: no UV + acetone; Lane 2: no UV + acetone; Lane 3: UV + acetone; Lane 4: UV + genistein. Thus even post-exposure treatment was shown to inhibit c-*fos* and c-*jun* expression.

Example 5

This experiment was reported in. Inhibitory effect of genistein on a tumor promotor-induced c-*fos* and c-*jun* expression in mouse skin, Wei et al., Oncology Reports 3:125-128, 1996.

Figure 4 shows that topical application of a promoting dose (8.5 nmol) of TPA significantly induces expression of c-*fos* and c-*jun* mRNA in mouse skin (lane 3) compared to the acetone-treated control (lane 1). As reported by Zwiller et al., Inhibition of PDGF-induced c-*jun* and c-*fos* expression by a tyrosine protein kinase inhibitor, Oncogene 6:219-221, 1991, there are two c-*jun* mRNA fragments (2.7 and 3.2 kb, respectively), which is due to the presence of two polyadenylation signals. Densitometric quantitation indicates that TPA significantly increases expression of these protooncogenes by 1.7-(c-*jun* 3.2 kb), 3.2-(2.7 kb c-*jun*), and 7.0-fold (c-*fos*), respectively, as compared to the acetone-treated control. Treatment of mouse with genistein alone slightly decreases the basal levels of c-*fos* and c-*jun* mRNA (lane 2; 10 μmol genistein/acetone). However, pretreatment of mouse skin with genistein suppresses TPA-induced expression of both c-*fos* and c-*jun* (lane 4: 1 μmol genistein/TPA; lane 5: 5 μmol genistein/TPA; and lane 6: 10 μmol genistein/TPA). Suppression of c-*fos* expression by genistein is more pronounced than that of c-*jun*, and at a dose of 10 μmol genistein, TPA-induced c-fos expression is almost completely inhibited. Hybridization with a cyclophilin probe indicates that mRNA for the tested samples are equally loaded.

Figure 5 shows the quantitation of transcript levels of c-*jun* and c-*fos* from three independent experiments. All results were normalized by their corresponding cyclophilin intensity, and then versus the acetone treated control. The final results were expressed as the intensity ratio (treated groups vs. controls). The background intensity of acetone-treated control was 3.2 ± 4.9 (c-*fos*), 5.0 ± 1.8 (3.2 kb c-*jun*) and 9.1 ± 3.9 (2.7 kb *c-jun*). Expression of both 3.2 kb and 2.7 c-*jun* mRNA

message is only weakly inhibited by about 20% at a high dose (10 μmol) of genistein. In contrast, genistein strongly inhibits the TPA-induced expression of c-*fos* in a dose-dependent manner with an apparent IC_{50} of 6.5 μmol genistein.

Figure 6 shows the effect of 10 μmol genistein on TPA-induced c-*fos* expression at different dosing times. Genistein was topically applied to mouse skin 30 min. before, simultaneously or 30 min. after 5 μg TPA treatment. Mice were sacrificed 2 h after TPA treatment and skin mRNA was purified. Protooncogene expression was analyzed by the Northern hybridization. A, c-*fos* and B, cyclophilin. Samples: Lane 1, acetone/acetone; lane 2, acetone/TPA; lane 3, 10 μmol genistein applied 30 min before TPA; lane 4, 10 μmol genistein applied simultaneously with TPA; and lane 5, 10 μmol genistein applied 30 min after TPA. The results show that TPA significantly induces c-fos expression (lane 2) compared to acetone-treated control (lane 1). Genistein can significantly inhibit TPA-induced c-fos expression independent of the different dosing schedules (lanes 3-4).

Example 6

The various methods and compositions by which genistein may be topically applied are not limited by the present disclosure. The following is a representative list of suitable compositions:

1) 0.1-5 μmol genistein/cm^2 in 5:95 DMSO:acetone.
2) 0.1-5 μmol genistein/cm^2 in 30:70 propylene glycol:ethanol.
3) 0.1-5 μmol genistein/cm^2 in 2:80 Twean 80:water.
4) 0.1-1 μmol genistein/cm^2 in combination with para-aminobenzoic acid (to absorb UVB).
5) 0.1-1 μmol genistein/cm^2 in combination with benzophenone derivatives (oxybenzone, dioxybenzone - to absorb UVB and UVA).
6) 0.1-1 μmol genistein in combination with titanium dioxide and/or zinc oxide.

7) 0.1-1 μmol genistein in combination with vitamins with antioxidant properties, such as vitamin A, vitamin C and vitamin E, including such vitamins in cosmetic moisturizing creams or skin care lotion, particularly for post-UV exposure.

8) 0.1-1 μmol genistein in combination with other natural products, such as squalene from shark liver oil and aloe vera from liliaceae in cosmetic product.

9) 0.1-5 μmol genistein added to low SPF sunblocker cream, now commercially available.

10) 0.1-5 μmol genistein with alphahydroxy acids.

11) 0.1-5 μmol genistein with Retin-A.

12) 0.1-5 μmol genistein with betacarotene.

CLAIMS

1. A method of inhibiting the harmful effect of UVR exposure to the human skin comprising topically applying a therapeutically effective amount of genistein to the skin at a time sufficiently close to the time of UVR exposure to inhibit UVR-induced damage to the skin.

2. A method according to claim 1, comprising applying genistein to the skin prior to exposure.

3. A method according to claim 2, comprising applying genistein to the skin within two hours prior to exposure.

4. A method according to claim 1, comprising applying genistein within two hours of exposure.

5. A method according to claim 1, comprising applying genistein in an amount of at least 0.1 μmol/cm^2 of skin.

6. A method according to claim 1, wherein the genistein is mixed with a carrier in a concentration of from 0.1 to 1.0 μmol/cm^2.

7. A method according to claim 1, wherein the genistein is mixed with a composition having cosmetic or medicinal properties in a concentration of from 0.1 to 1.0 μmol/cm^2.

8. A method according to claim 1, wherein the genistein is mixed with at least one of the following: dimethyl sulfoxide; dimethylsulfoxide:acetone; Twean 80; Twean 80:water; para-aminobenzoic acid; benzophenone derivatives; titanium dioxide, zinc oxide; antioxidant vitamins including vitamins A, C and E; cosmetic moisturizing cream, skin care lotions,

squalene; aloe vera; sunblock cream; lipid; alphahydroxy acids; Retin-A; betacarotene.

9. A method according to claim 1 of mitigating the cancer-inducing effect of UVR, comprising topically applying an amount of genistein sufficient to inhibit UVR-induced skin photocarcinogenesis.

10. A method according to claim 1 of inhibiting the skin photo aging effect of UVR, comprising topically applying an amount of genistein sufficient to inhibit UVR-induced aging.

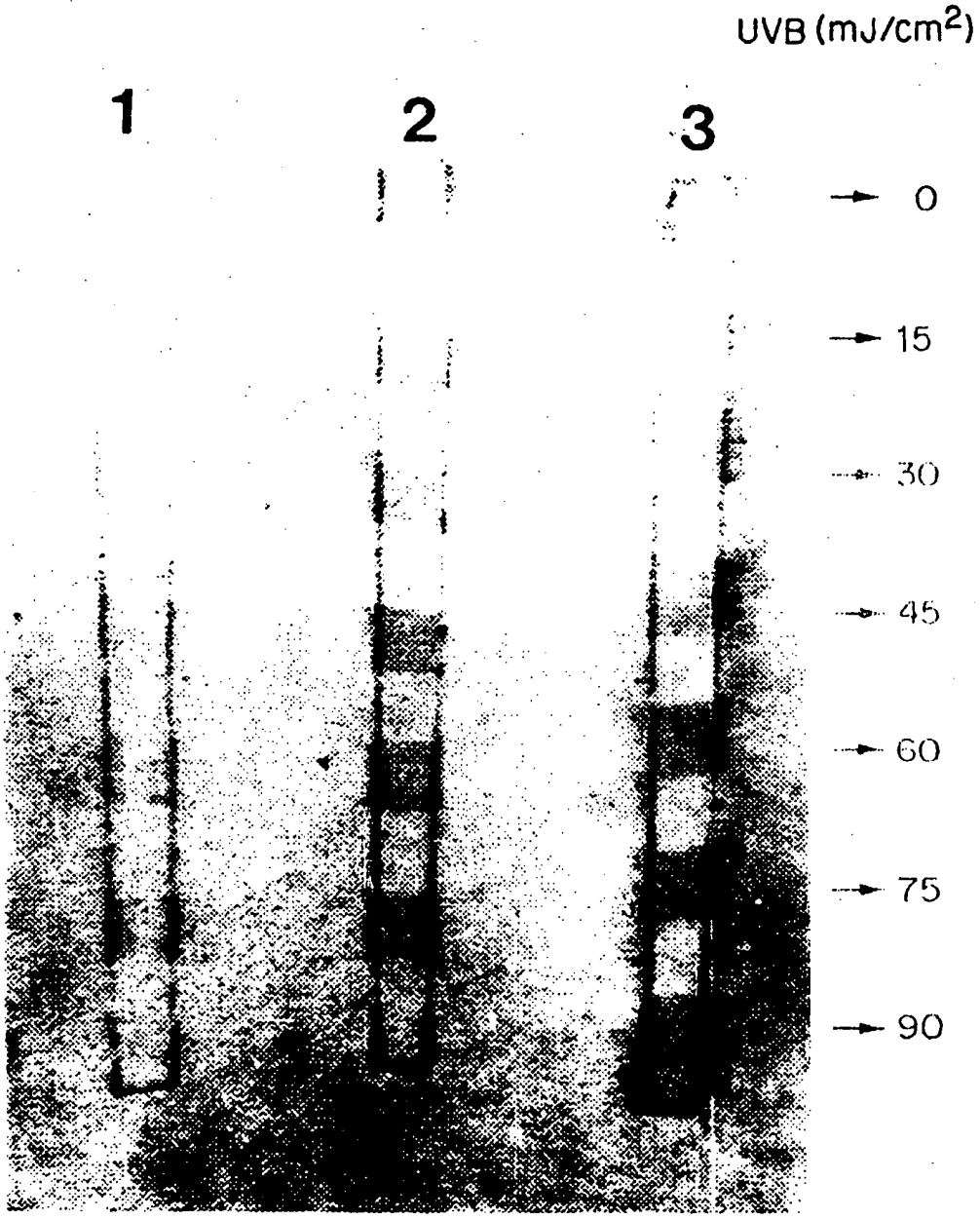

FIG. 1

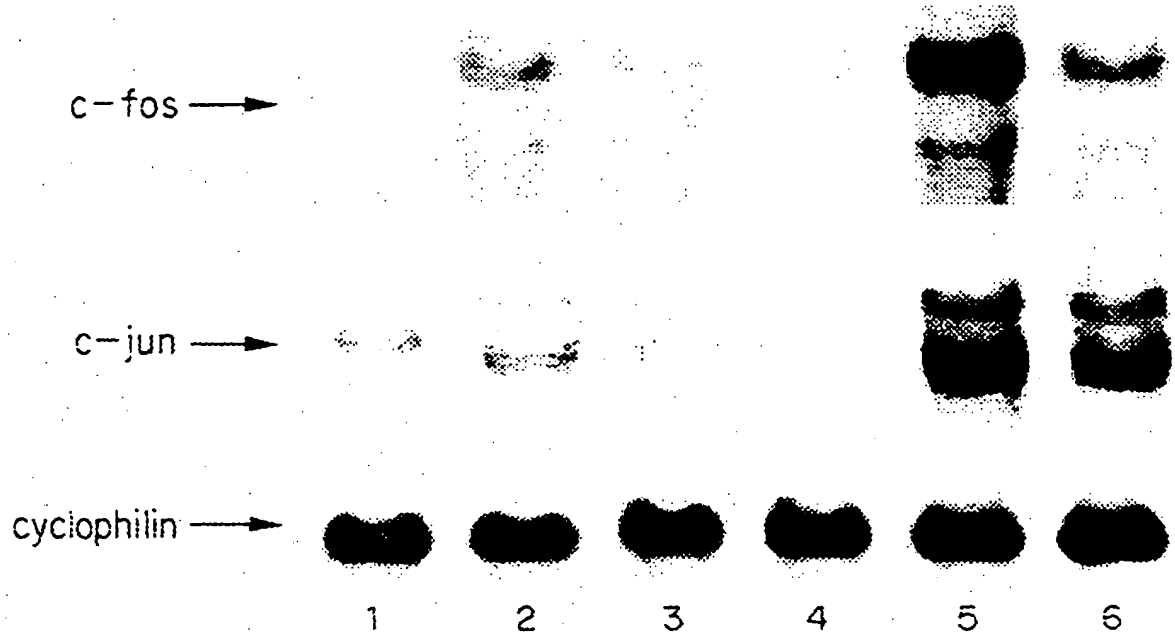

FIG. 2

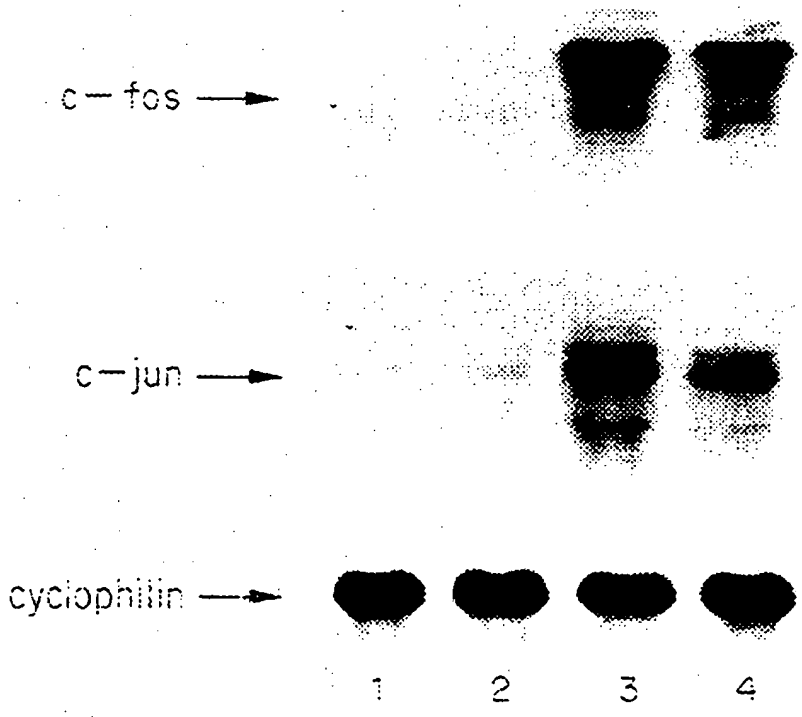

FIG. 3

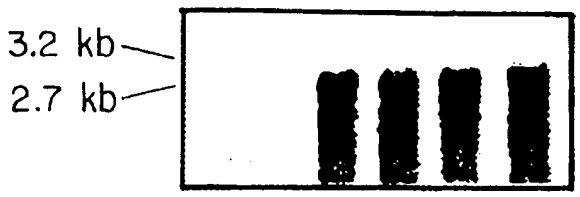

FIG. 4A

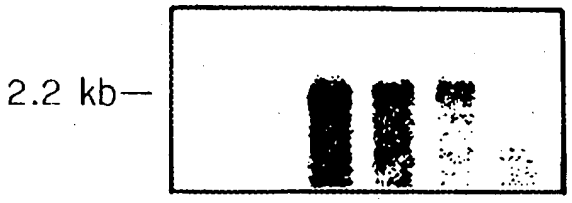

FIG. 4B

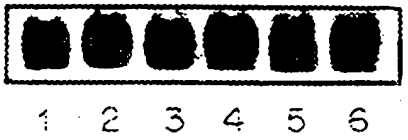

FIG. 4C

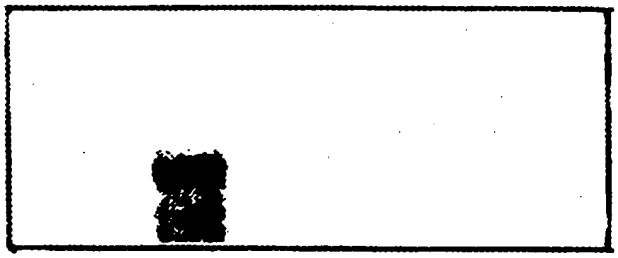

FIG. 6A

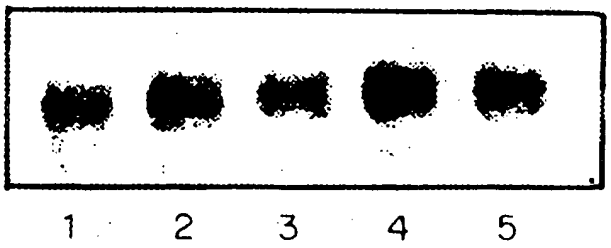

FIG. 6B

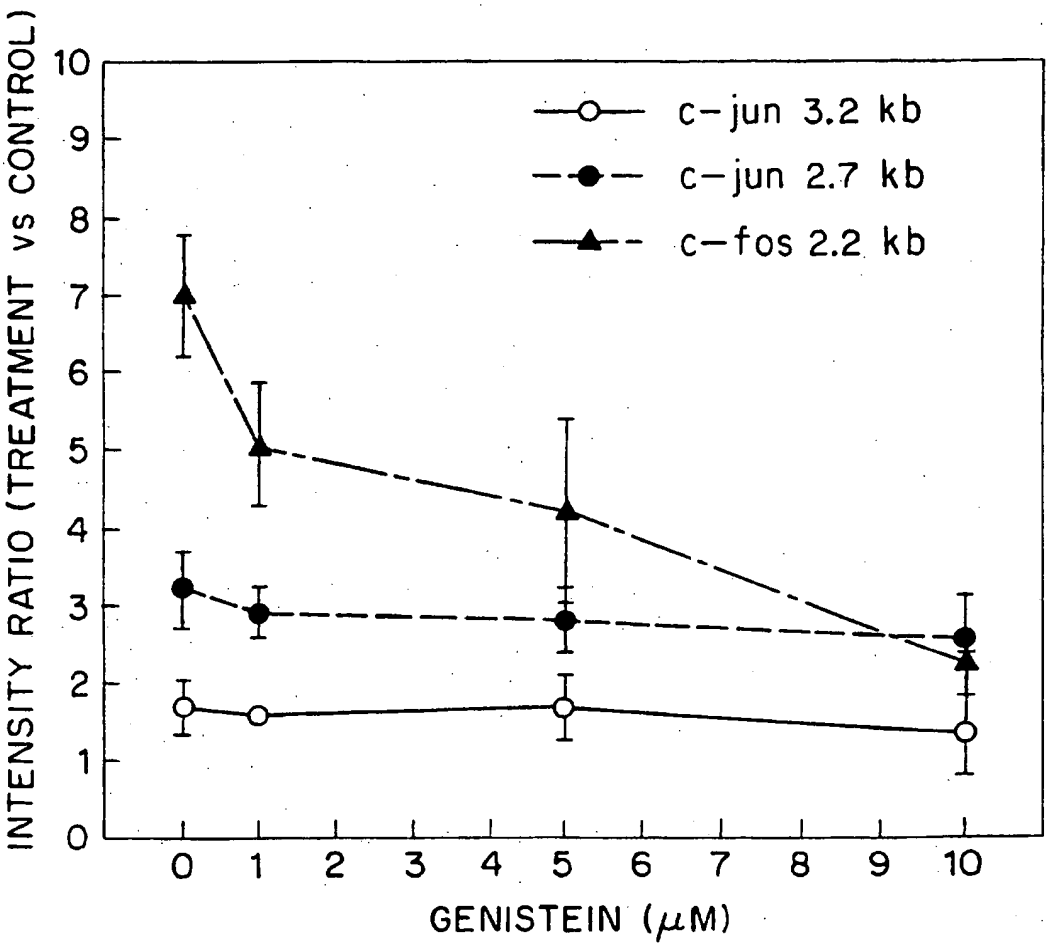
INTENSITY RATIO (TREATMENT vs CONTROL)
0
1
2
3
4
5
6
7
8
9
10
c-jun 3.2 kb
c-jun 2.7 kb
c-fos 2.2 kb
0 1 2 3 4 5 6 7 8 9 10
GENISTEIN (μM)

FIG. 5

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 7/42, 7/48

A3

(11) International Publication Number: **WO 97/46208**

(43) International Publication Date: 11 December 1997 (11.12.97)

(21) International Application Number: PCT/US97/11963

(22) International Filing Date: 9 June 1997 (09.06.97)

(30) Priority Data:
08/657,915 7 June 1996 (07.06.96) US

(71) Applicant: MT. SINAI SCHOOL OF MEDICINE OF THE CITY OF NEW YORK [US/US]; One Gustave L. Levy Place, New York, NY 10028-6574 (US).

(72) Inventor: WEI, Huachen; 114-15 Union Turnpike, Forest Hills, NY 11375 (US).

(74) Agent: CLARK, Richard, S.; Brumbaugh, Graves, Donohue & Raymond, 44th floor, 30 Rockefeller Plaza, New York, NY 10112 (US).

(81) Designated States: AU, CA, GB, IL, JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
19 February 1998 (19.02.98)

(54) Title: GENISTEIN AS A PREVENTIVE AGAINST ULTRAVIOLET INDUCED SKIN PHOTODAMAGE AND CANCER

(57) **Abstract**

A method of inhibiting the harmful effect of UVR exposure to the human skin comprising topically applying a therapeutically effective amount of genistein to the skin at a time sufficiently close to the time of UVR exposure to inhibit UVR-induced damage to the skin. The genistein appears to act as a chemo preventative agent since it has no appreciable sun blocking effect. The genistein may be mixed with a variety of carriers and skin treatment compositions.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PC /US 97/11963

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/42 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 44 32 947 A (NEW STANDARD GMBH) 21 March 1996 see the whole document ---	1-10
X	PATENT ABSTRACTS OF JAPAN vol. 009, no. 192 (C-296), 8 August 1985 & JP 60 061513 A (SANSHIYOU SEIYAKU KK), 9 April 1985, see abstract --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 1997	30/12/1997

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sierra Gonzalez, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/11963

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	H. WEI: "Inhibitory effect of genistein on a tumor promoter-induced c-fos and c-jun expression in mouse skin" ONCOLOGY REPORTS, vol. 3, no. 1, 1996, pages 125-128, XP002048780 see page 126, column 1, line 25-34 see page 128, column 1, line 40-43 see abstract	1-3,7,9
X	N.S. LARSEN: "Differentiation Agents Yield Treatment, Prevention Options." J. NATL. CANCER INST., vol. 85, no. 23, 1993, pages 1900-1902, XP002048781 see page 1900, column 1, line 1-6 see page 1901, column 3, line 29-36	1,9
X	H. WEI: "Antioxidant and Antipromotional Effects of the Soybean Isoflavone Genistein" PROCEEDINGS OF SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, vol. 208, 1995, pages 124-130, XP002048782 cited in the application see page 127, column 2 see page 128, column 2, line 1-15 see figure 4	1,9

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte· ·ional Application No
PC·/US 97/11963

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 4432947 A	21-03-96	NONE	